## An amyloid-notch hypothesis for Alzheimer's disease.

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**Public Summary:**
Considerable effort has been spent examining the pathological consequences of amyloid-beta in all its different forms, but the physiological, non-pathological, role of this peptide has remained unclear. Here I discuss notable overlap between the signaling pathways used to regulate blood vessels and the enzymes used to generate amyloid-beta, a key feature of Alzheimer's disease pathology. A key feature of both mechanisms is gamma-secretase complex, which it the last step in producing amyloid-beta peptide. I hypothesize that during Alzheimer's disease there is feedback inhibition of the gamma-secretase complex due to high levels of amyloid-beta. A consequence of this effect is the stimulation of blood vessel branching and sprouting. Alzheimer's disease pathology includes areas of densely branched blood vessels that appear to be the result of dysfunctional angiogenesis.

**Scientific Abstract:**
For more than 20 years, the amyloid hypothesis has provided an important framework for Alzheimer's disease (AD) research, yet after 50,000 papers, the nonpathological function of beta-amyloid (Abeta) remains enigmatic. This mystery is compounded by an absence of gross abnormalities in amyloid precursor protein (APP)-deficient mice and zebrafish even though APP has been highly conserved throughout vertebrate evolution. Here, the author hypothesizes that vertebrate cells express APP and release Abeta as part of a mechanism to optimize blood vessel density with the metabolite removal needs of local tissue neighborhoods. High-gain feedback of Abeta production at the rate-limiting gamma-secretase step reduces Abeta production and Notch activation. Notch inhibition causes endothelial cells to adopt a tip cell morphology that induces more highly branched blood vessels. In vivo, gamma-secretase inhibitors block Notch signaling and induce dense capillary networks that are similar to those in the brains of AD patients and mice. Notch inhibition could also contribute to synapse loss by reducing EphB2 receptor expression. EphB receptors are critical for the maintenance of dendritic spine morphology, and deficiencies result in immature spines that lack synaptic activity. This revised amyloid-Notch hypothesis may also explain the disappointing results of recent clinical trials with gamma-secretase inhibitors.